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CORRECTION.

Boots Pure Drug Co. wish attention to be drawn to the fact that they do not manufacture "Hydroderm" as stated in the paper by Calnan and Sarkany (1958) *Brit. J. Derm.* **70**, 437. This preparation is made by Upjohn's of England Ltd.

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THE hydrogen ion concentration of the skin surface, determined in pH units, provides a potentially useful measurement for aetiological studies of skin disorders. At present, the interpretation of differences in average pH levels between groups of patients with different diseases and between affected and unaffected body areas in patients with the same disease is handicapped by an almost complete lack of information about the variation in pH levels in "normal" individuals, i.e. those with no skin disorders, and in different areas of the body surface of such "normals". In this paper we have tried to provide information for infants in their first week of life. Mean pH levels have been estimated, with reasonable precision, at thirty-four body sites in 203 children who had no apparent skin disease. Variation between infants, sexes and sites has been examined.

REVIEW OF THE LITERATURE.

Among the published aetiological studies, some of the conclusions of Levin and Silvers (1932), Anderson (1951) and Schmid (1952) are relevant to the present work.

Levin and Silvers (1932), using a quinhydrone electrode potentiometer with a gold electrode, showed that patients with acute or sub-acute eczematous conditions had a neutral rather than acid skin surface. In chronic eczematous conditions with lichenification and scaling the change from an acid reaction was slight, but in erythroderma a very alkaline level was reached. Approximate levels of 5.0 to 5.3 pH units were suggested as typical of the skin surface

of healthy persons, but the existence of variation between body areas was emphasized. For example, the intertriginous areas were more acid than others and specifically the skin of the chest was more acid than that of the axillae. They suggested that their observations were compatible with the conclusion that the hydrogen ion concentration depended upon an intact keratin layer and the chemicals of evaporated skin secretions, principally sweat.

Anderson (1951), using a Cambridge pH meter with a sealed glass electrode, made pH determinations at a variety of body sites on fifty affected and fifty unaffected children, aged one month to twelve years. She concluded that children with seborrhoeic dermatitis had a raised pH over the whole body surface, but children with Besnier's prurigo or facioflexural eczema had a raised pH only at affected areas. She discussed the aetiology of infantile eczema and drew attention to the tendency of the seborrhoeic child to develop secondary infection, even in the absence of eczematous lesions. She suggested that it was this quality of the skin which was associated with the alkaline reaction over the whole body surface of such children. The range of her normal series was from 4.0 to 6.0 pH units, again with noticeable variation over the whole body surface.

Schmid (1952) made comparative estimates of pH and of the acid and alkali neutralizing power of the skin of persons with and without skin lesions. His pH determinations on unaffected subjects and on many with eczema were in the range of 4.8 to 5.8 units, but most of his patients with seborrhoeic dermatitis and some with generalized eczema had higher pH levels.

More relevant to the present work are the studies of Bergeim and Cornbleet (1947), Blank (1939a, b, c and d) and Behrendt and Green (1958); these refer mainly to persons with no skin disorders. Bergeim and Cornbleet (1947), from scalp washings and by direct determinations with glass or antimony electrodes, found pH values for the scalps of sixty young men and women between 4.3 and 6.1 pH units. Although no "uniform relationship" between acidity and seborrhoea was detected, they thought that a temporary reduction in acidity of the scalp could be achieved by washing. The most painstaking studies were undertaken by Blank (1939a, b, c and d), who reported means and standard deviations of the pH of the skin surface at different sites on the arms of children and on the arms, foreheads and necks of adults. He used a glass electrode (Blank, 1939a) on 100 male medical students aged 20 to 27 years, 100 female nurses aged 19 to 26 years (Blank, 1939b) and 100 boys and 100 girls, who were hospital patients aged 3 to 14 years (Blank, 1939c). None of his subjects had any skin disorder. His main conclusions were the following.

1. The pH determinations ranged from 4.0 to 7.0 pH units, although most were between 4.2 and 5.6 pH units in adults and 4.2 and 6.0 pH units in children.

2. The pH determinations in females had a wider range than those in males.

3. The mean pH estimate in females was slightly greater than that in males, by about 0.5 pH units in adults and 0.3 pH units in children.

4. The extensor surfaces of the arm had a slightly higher mean pH estimate than the corresponding flexor surfaces.

5. The mean pH estimate of the antecubital area was lower than that for any other arm surface.

6. The mean pH estimate in boys was slightly greater than that in men, but this apparent age difference was not observed in females.

Behrendt and Green (1958) made 945 pH determinations on 109 boys and 113 girls; they included three body surfaces, the axilla, shoulder and abdomen, and in 27 they made repeated serial determinations at each site. The children included 64 Caucasians, 60 Negroes and 98 Puerto Ricans, none of whom had any skin disorder. They used the colorimeter method devised by Bernstein and Herrmann (1942) as modified by Herrmann, Behrendt and Karp (1946) and Behrendt and Green (1955). Some of the determinations were checked with a Beckman pH meter with a special glass electrode. By comparing children in different age groups, they detected an association between age and pH in early life. In the first twenty-four hours of life, the pH of the skin surface indicated a markedly alkaline state; only 15 of 109 determinations were of less than 6.0 pH units. In successively older age groups, the mean pH fell rapidly to a level between 4.0 and 5.0 pH units by the end of the fourth day. Later, there was little difference in the mean pH level. In the axilla, the mean pH of children aged one to forty-eight hours was 6.3 pH units, compared with 5.0 in those aged three to six days and 4.7 in those aged seven to thirty days. Similar age trends were observed in the determinations on the shoulder and abdomen, although the absolute levels were lower on the shoulder than in the axilla and higher on the abdomen than in the axilla. The minimum mean pH was less rapidly reached on the abdomen than in the other areas. The results of repeated estimations in the twenty-seven children were compatible with the average findings in different children at different ages. In the authors' opinion, the trends with age were not materially affected by race and sex, or by skin washing prior to pH estimation. They suggested that "the low skin acidity observed during the newborn period is most likely caused by the neutralizing influences of the vernix caseosa. It appears that the shift from more alkaline to acid pH values is directly related to the gradual transition to a normal skin surface."

These results are very relevant to the present work, but unfortunately the report by Behrendt and Green (1958) was not published until after our own work was completed. Thus we were unable to profit by their experience in the design of our experiment. Nevertheless, we have considered the implications of their conclusions upon the interpretation of our results in appropriate sections of the present report.

EXPERIMENTAL DESIGN.

Theoretical considerations.

Our own interest in this subject stemmed from the possible clinical use which might be made of determinations of the pH of the skin surface, both in aetiological studies of infantile eczema and as a means of identifying susceptible groups of infants (Beare, Cheeseman, Gailey and Neill, 1958). We felt handicapped by the paucity of information about the "natural" variation in the pH of the skin surface in "normal" children without skin disease. It seemed important to us to establish the average pH and the dispersion of individual observations about the average for a large number of body sites and to establish the kind of variation which might reasonably be expected to occur between body sites. The theoretical requirements for such a study demand groups of children of each sex, sampled at random from the total population of children without skin disease so as to be representative of that population. The size of such groups must be large enough to give reasonably precise estimates for that population. Moreover, in order to achieve comparability between children and between sites, all determinations must be made with a minimum of observer error, preferably achieved by the same observers using the same apparatus and technique in similar environmental conditions. In what follows, we describe the procedure and results obtained in an experiment designed to attain these theoretical requirements, as nearly as was practically possible with the time and resources at our disposal.

Terminology.

The symbol pH represents the logarithm (to base ten) of the reciprocal of the hydrogen ion concentration of a solution. In a neutral solution with equal numbers of hydrogen and hydroxyl ions, $\text{pH} = 7.00$ so that solutions with pH less than 7.00 units are acid and those with pH greater than 7.00 units are alkaline. It is customary to refer to these logarithms as "pH units"; all determinations and estimates in this work are so measured and for brevity "pH units" should be taken as read after all such values.

Blank (1939a) pointed out that pH determinations made on the skin surface have been referred to as "pH of the skin", "pH of the skin surface" and as a variety of other terms. He suggested that in fact the determination made was probably that of the pH of the aqueous solution bathing the cells of the semi-solid skin tissue. To avoid tedious repetition, our determinations are referred to simply as pH, qualified by the anatomical description of the body surface concerned.

In the text and tables, where an estimate is followed by $\pm$, the value following this sign is the standard error of the estimate preceding it. The estimate $\pm$ a multiple (approximately equal to two) of the standard error gives the 95% confidence limits for the statistic estimated. Thus a mean pH shown as 7.0 ± 0.05 indicates 95% confidence limits of 6.9 to 7.1. The multiple of the standard error used for this calculation depends ultimately upon the number of determinations from which the mean was estimated. The 95% confidence limits of, say a mean, are the limits within which the true mean, for the population from which the sample is drawn, is likely to lie and 95% of such generalizations from sample to population are likely to be valid. Dispersion of determinations about a mean are indicated by the standard deviation and reference will be made to the variance which is the square of the standard deviation. Results unlikely to arise by chance more than once in twenty trials ($P < 0.05$) are conventionally said to be "significant". This word is used only in this technical way so that results may be described as significant even though they are clinically or aetiologicaly unimportant. These statistical considerations are based on certain assumptions about the distribution of pH determinations and subgroup means. In most instances the assumption is that the distributions are normal and tests which justify this are included where appropriate.

Selection of subjects.

Blank's (1939c) results showed the variance of pH determinations on the arm to be between 0.16 and 0.36 for boys and 0.25 and 0.49 for girls. From this, we reckoned that one hundred infants of each sex would yield means with standard errors of about ± 0.07 , and therefore with 95% confidence limits of not more than the estimated mean ± 0.14 , for any single body site and sex. In view of the accuracy of the proposed method of pH determinations, estimated at ± 0.20 pH units, and the time available for the work, we considered such confidence limits sufficiently precise for all likely practical applications of the results.

In the hope of eliminating the effect of age on pH observed by Blank (1939c) and because of our interest in infantile skin disease, we decided to restrict the survey to children in a narrow age group early in life and the age group of one to seven days was chosen as most suitable. In view of the subsequent findings of Behrendt and

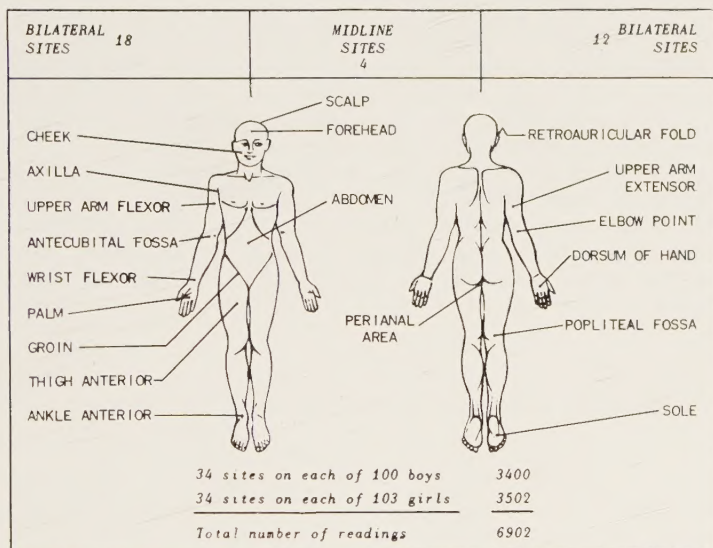


FIG. 1.

Green (1958), it would have been wiser to have chosen a slightly later age group. In fact, the decision to use the chosen age group was influenced also by the ease of access to children in a local maternity hospital. Although "hospital births" could not be considered as representative of a wider population of children for many purposes, it was agreed that pH was unlikely to be influenced by such factors as parity, age of mother or others which determine institutional, rather than domiciliary, delivery. Indeed, the advantages of making determinations on children in hospital were considered to outweigh any possible bias that might result in generalizations from the sample, since the environmental conditions under which all determinations could be made and the care of the infants were much more uniform than would obtain if determinations were made in the infants' own homes.

Consequently, the same two members of the team with the same apparatus visited the same ward of one local maternity hospital every Tuesday morning after a given date. At each visit all children were examined for skin disease (none was found) and pH was determined by the technique described in the next section at the thirty-four body sites shown in Fig. 1 and listed in Table I. At each visit, all children in the required age group who had not been previously examined were included and the

visits continued until at least one hundred children of each sex were examined. The final series consisted of thirty-four pH determinations for each of 100 boys and 103 girls. The skin was not prepared in any way before the readings were taken. The infants had not been washed for several hours previously.

Method of determination of pH.

Determination of pH was made by two observers using a Marconi direct reading pH indicator. In work with young children a direct reading technique was more convenient than a potentiometric method as the former was more rapid. The instrument was easily set up and remained stable for about three hours; the scale could be read accurately to ± 0.1 . The glass electrode was a Stadie type micro-glass bulb, used in conjunction with a micro-calomel electrode manufactured by the Doran Instrument Company. The micro-calomel electrode terminated in a glass capillary which was moistened with saturated potassium chloride in the electrode container. The tip of the micro-calomel electrode was approximated to within 5 mm. of the micro-glass electrode bulb by means of a small rubber band; thus the area of contact with the skin was very small. Both electrodes were fitted with 6-ft. leads for connection with the pH meter so that determinations of pH at all areas of the body could be made conveniently in about five minutes.

For a given series of determinations, the instrument was standardized using a potassium phthalate buffer of pH 4.0. After standardization, the electrode system was kept in a small jar of distilled water into which it was dipped between each determination. Throughout, one observer applied the electrodes while the other made the readings on the pH meter. A photograph of the electrode system has been published (Beare *et al.*, 1958).

TABLE I.—*Site and Sex-site Means (in pH units).*

Site	Sex-site means				Site means	
	Males (100 boys)		Females (103 girls)		Both sexes (203 children)	
			<i>Bilateral sites</i>			
	Left	Right	Left	Right	Left	Right
Retroauricular fold	6.01	6.19	6.00	6.19	6.01	6.19
Cheek	6.21	6.34	6.09	6.16	6.15	6.25
Axilla	6.31	6.11	6.17	6.12	6.24	6.12
Upper arm flexor	6.27	6.25	6.07	6.14	6.17	6.19
Upper arm extensor	5.75	5.65	5.76	5.55	5.75	5.60
Antecubital fossa	6.30	6.43	6.25	6.33	6.28	6.38
Elbow point	5.64	5.56	5.56	5.57	5.60	5.57
Wrist flexor	5.91	6.12	5.88	5.91	5.89	6.01
Dorsum of hand	5.62	5.69	5.50	5.59	5.56	5.64
Palm	6.08	6.23	6.05	6.15	6.07	6.19
Groin	6.83	6.50	6.75	6.50	6.79	6.50
Thigh anterior	6.52	6.19	6.26	5.93	6.39	6.06
Popliteal fossa	5.96	5.88	5.95	5.81	5.96	5.85
Ankle anterior	6.18	5.93	6.17	5.86	6.17	5.89
Sole of foot	6.16	6.03	6.18	6.03	6.17	6.03
<i>Other sites</i>						
Scalp		6.64		6.48		6.56
Forehead		6.48		6.35		6.42
Abdomen		6.10		5.87		5.99
Perianal area		6.02		6.05		6.03

ANALYSIS OF RESULTS.

Classification of determinations.

In all, 6902 pH determinations were made. One at each of the 34 sites on each of 100 male subjects, yielded 3400 and one at each of the 34 sites on each of 103 female subjects yielded 3502. It is convenient to consider the following sub-group means.

1. Sex means, of which there are two, are based on 3400 determinations in boys and 3502 in girls ; the sex means are 6.12 for boys and 6.04 for girls.

2. Site means, of which there are 34 ; each is based on 203 determinations. These means are shown in the last two columns of Table I.

3. Subject means, of which there are 203 ; each is based on 34 determinations. The distribution of the subject means is shown in Table II.

TABLE II.—*Distribution of Subject Means.*

Subject mean (pH units).	Number of subjects.
4.25-	1
4.50-	—
4.75-	2
5.00-	7
5.25-	17
5.50-	30
5.75-	36
6.00-	37
6.25-	29
6.50-	19
6.75-	15
7.00-	7
7.25-	—
7.50-	1
7.75-	1
8.00-	1
Total	203

4. Sex-site means, of which there are 68 ; each of the 34 relating to males is based on 100 determinations and each of the 34 relating to females is based on 103 determinations. These means are shown in the first four columns of Table I.

Analysis of variance.

The design of this experiment permits examination of the variation between the sub-group means by analysis of variance. The appropriate analysis, as a "split plot design", is fully described by Cochran and Cox (1957), among others. The analysis is shown in Table III from which the following conclusions are justified.

TABLE III.—*Analysis of Variance of 6902 pH Estimates.*

Source of variation.	Sum of squares (pH units) ² .	Degrees of freedom.	Mean square (pH units) ²	Variance ratio F.
<i>Between subjects</i>				
Sexes . . .	12.32	1	12.32	F = 1.16, P > 0.20
Residual . . .	2141.49	201	10.65*	—
<i>Within subjects</i>				
Sites . . .	574.68	33	17.41	F = 44.64, P < 0.001
Sites × sexes . . .	11.69	33	0.35	F = 1.11, P > 0.20
Residual . . .	2572.13	6633	0.3878†	—
Total . . .	5312.31	6901	—	—

* Males 10.42, Females 10.88, F = 1.04, P > 0.20.

† Males 0.38, Females 0.39, F = 1.03, P > 0.20.

1. The variation in pH determinations in males is not significantly different from that in females.

2. The difference between the sex means is not significant.

3. The interaction between site and sex is not significant, so that the differences between sex-site means for any given site are probably not significantly different.

4. The differences between site means are significant, but this does not exclude the possibility that there may be groups of site means which are very similar.

However, a comparison between two groups of subjects at these ages could be invalid if their age distributions are materially different because of the association between age and pH which was demonstrated by Behrendt and Green (1958). Thus if one group contained a higher proportion of children aged one day than the other, the former group would be expected to have a higher mean pH than the latter because of the high pH determinations peculiar to the first day of life. Now there were 6 boys and 6 girls in their first day of life in the 203 children, so that the influence of the high pH values at this age is unlikely to make any great difference to the sex comparison. In fact, the mean age of the boys is 4.1 days compared to 3.6 days for the girls. The difference is not significant ($0.10 > P > 0.05$). Moreover, when the male and female distributions by age are compared they are found to be very similar ($0.50 > P > 0.30$). Thus it is unlikely that the difference between the mean pH of boys and girls is influenced by age differences between the sexes so that, with reasonable confidence, we can conclude that sex plays no part in determining the average pH of the whole body area in so far as it is represented by the sites considered here.

The minimum significant differences between two sub-group means which are likely to be detected by this analysis are 0.15 between two sex means, 0.12 between two site means, 0.17 between two sex-site means relating to the same sex and 0.23 between two sex-site means relating to opposite sexes. Thus, quite small differences in mean pH between sub-groups are likely to be detected

as significant if, in fact, they exist. It is unlikely, therefore, that any mean differences of clinical or aetiological importance will not be isolated, but possibly several detected significant differences will be clinically unimportant. With these considerations in mind, the various sub-group means can be considered in more detail.

Sex-site means.

Although the analysis of variance suggests that, at the ages concerned, sex plays no important part in determining pH levels, an examination of Table I must be made in view of Blank's (1939b) contrary conclusion about older children. He suggested that for arm sites the mean pH of girls was about 0.3 greater than that of boys.

Table I shows that in 26 of the 34 sites the mean pH of boys is greater than that of girls. This is significantly more than the 17 sites which might be expected by chance if there was no sex difference ($0.01 > P > 0.001$). Thus it may be true that some small differences do exist, but if so, they are opposite to those observed by Blank, and in view of the results of the analysis of variance must be negligible in size. Indeed, inspection of the table shows that the maximum difference between sex-site means, of corresponding site but opposite sex, is only 0.26 and occurs at both the left and right anterior thigh. Only these two sites give a difference in excess of the minimum significant difference (0.23) likely to be detected and 2 significant differences out of 34 comparisons (i.e. 6%) is not incompatible with the criterion of significance ($P < 0.05$ or 5%) used in this work. What is surprising, on a null hypothesis, is that both differences mentioned should occur at the same body site, and that in both, the boys' mean should be the greater. In what follows, no further distinction between the sexes is made because in terms of averages, it is most unlikely that sex has any material effect on the conclusions drawn.

Subject means.

Table II gives the distribution of the 203 subject means. These range from 4.37 to 8.21, with a grand mean of 6.08 and a standard deviation of 0.56. The grand mean, 6.08, is almost identical with the median value, 6.06, and the distribution of the subject means does not appear to depart much from what might be expected, if, in the general population of children of this age, pH determinations were normally distributed. On the hypothesis of a normal distribution the statistics $g_1 = g_2 = 0$ estimate skewness and kurtosis respectively (Snedecor, 1956). The distribution of Table II gives $g_1 = 0.59 \pm 0.17$ and $g_2 = 2.42 \pm 0.34$ and both values differ significantly from zero ($P < 0.001$). This implies that the observed distribution is asymmetrical, with an excess of observations at the lower pH values, and is more peaked than a normal distribution, with an excess of observations at the extreme pH values. This

departure from normality arises largely because of the tail of the observed distribution at the higher pH values. If the subject with the highest mean pH (8.21) is omitted then, $g_1 = 0.18 \pm 0.17$ and $g_2 = 0.28 \pm 0.34$ and neither are significantly different from zero ($0.30 > P > 0.20$ and $0.50 > P > 0.40$ respectively). It seems reasonable to conclude that the mean pH of infants of this age is distributed, if not precisely, then very closely in accordance with a normal distribution.

Site means.

The most dramatic variation indicated by the analysis of variance is that between the site means. The inference is that the body surface is not uniformly acid or alkaline and that different areas have different reactions. The lowest site mean is 5.56 and the highest 6.79, as can most conveniently be seen from Table IV where the 34 sites are arranged in order of their site means from

TABLE IV.—*Sites Ranked in Order of Site Means.*

Rank order.	Site (R = Right, L = Left).	Site mean (pH units).	Rank of homogeneous site means*
1	Dorsum of hand . . . L .	5.56 .	1
2	Elbow point . . . R .	5.57 .	2
3	Elbow point . . . L .	5.60 .	3
4	Upper arm extensor . . . R .	5.60 .	4
5	Dorsum of hand . . . R .	5.64 .	5 5
6	Upper arm extensor . . . L .	5.75 .	6 6
7	Popliteal fossa . . . R .	5.85 .	7 7
8	Wrist flexor . . . L .	5.89 .	8 8
9	Ankle anterior . . . R .	5.89 .	9 9
10	Popliteal fossa . . . L .	5.96 .	10 10 10
11	Abdomen	5.99 .	11 11 11
12	Retroauricular fold . . . L .	6.01 .	12 12 12
13	Wrist flexor . . . R .	6.01 .	13 13 13 13
14	Sole	6.03 .	14 14 14 14 14
15	Perianal area	6.03 .	15 15 15 15
16	Thigh anterior . . . R .	6.06 .	16 16 16 16 16
17	Palm	6.07 .	17 17 17 17 17
18	Axilla	6.12 .	18 18 18 18 18
19	Cheek	6.15 .	19 19 19 19 19
20	Upper arm flexor . . . L .	6.17 .	20 20 20 20
21	Sole	6.17 .	21 21 21 21
22	Ankle anterior . . . L .	6.17 .	22 22 22 22
23	Palm	6.19 .	23 23 23
24	Retroauricular fold . . . R .	6.19 .	24 24 24
25	Upper arm flexor . . . R .	6.19 .	25 25 25
26	Axilla	6.24 .	26 26
27	Cheek	6.25 .	27 27
28	Antecubital fossa . . . L .	6.28 .	28 28
29	Antecubital fossa . . . R .	6.38 .	29 29
30	Thigh anterior . . . L .	6.39 .	30 30
31	Forehead	6.42 .	31
32	Groin	6.50 .	32 32
33	Scalp	6.56 .	33
34	Groin	6.79 .	34

Standard error of a single site mean = 0.044.

* Each column shows ranks of means which are not significantly different by Duncan's (1955) test.

rank order 1, the lowest, to rank order 34, the highest. The standard deviation between the 34 site means is 0.29. No significant departure from normality can be detected in the distribution of the 34 site means as $g_1 = 0.04 \pm 0.40$ and $g_2 = 0.04 \pm 0.79$, neither g value is significantly different from zero ($P > 0.90$) although the number of sites is rather small for this test. The standard error of a single site mean is 0.0437. Thus for any one site the 95% confidence limits are the observed site mean ± 0.09 .

It is of clinical interest to study the differences between site means in some detail. Although the analysis of variance shows that significant differences exist, it throws no light on which sites are homogeneous (i.e., which have site means which are not significantly different) and which are heterogeneous (i.e., which have site means which are significantly different). Duncan (1955) has proposed "the new multiple range test" to identify homogeneous sub-group means in such experiments and the results of applying his test to the present data are summarized in the last column of Table IV. In this table the rank orders of homogeneous groups of site means appear in a single vertical column in the last major column of the table. For example, rank orders 1-5 form one homogeneous group, orders 5-6 another, 6-7 another, 7-10 another and so on. From this it follows that significant differences between site means can easily be detected because each member of a significantly different pair appears in a different homogeneous group. For example, rank orders 1-4 have significantly smaller means than any of the other thirty sites except rank order 5; rank order 5 has a significantly smaller mean than any order higher than 6, rank order 6 has a significantly smaller mean than any order higher than 7 and a significantly larger mean than any below order 5. The general continuous overlap of the homogeneous groups, their increase in size towards the middle rank orders and their subsequent decrease in size, are features compatible with the type of distribution already noted.

An examination of this section of Table IV reveals the following points of interest.

1. For 10 of the 15 bilateral sites no significant difference exists between the means on the right and left of corresponding sites. These are, the dorsum of the hand, elbow point, popliteal fossa, wrist flexor, sole, palm, axilla, cheek, upper arm flexor and antecubital fossa.
2. For 4 of the remaining 5 bilateral sites, the mean on the left side is significantly greater than that on the right. These, with the difference in brackets, are upper arm extensor (0.15), ankle anterior (0.28), thigh anterior (0.33) and groin (0.29).
3. For the remaining bilateral site the mean on the right side is significantly greater than that on the left. This site, with the difference in brackets, is the retroauricular fold (0.18).
4. Comparable flexor and extensor surfaces have significantly different site

means such that the flexor surface is always the greater. These, with the differences in brackets are palm and dorsum of the hand (left 0.51, right 0.55), antecubital fossa and elbow point (left 0.68, right 0.81) and upper arm extensor and flexor (left 0.42, right 0.59).

5. Similar significant differences exist between flexor and extensor surfaces, which though less well related, are anatomically approximate. These, with the differences in brackets, are wrist flexor and dorsum of the hand (left 0.33, right 0.37), axilla and upper arm extensor (left 0.49, right 0.52) and antecubital fossa and upper arm extensor (left 0.53, right 0.78).

6. On average, the most acid surfaces of the body are the dorsum of the hands, the elbow points and the upper arm extensors. All have site means of 5.75 or less and all except the left upper arm extensor comprise a single homogeneous group (rank orders 1-5). The left upper arm extensor has a mean not significantly different from that of the right dorsum of the hand but significantly lower than the means of all but one of the remaining 28 sites.

7. On average, the most alkaline surfaces of the body are the groins and the scalp and the forehead can be included in this group. The mean of the left groin is significantly greater than that of any other site, while that of the scalp is significantly greater than that of any site other than the groins. The mean of the right groin is significantly greater than that of any site other than the left groin, scalp, forehead, left thigh anterior and right antecubital fossa. Segregation of the sites at this end of the scale is difficult, but since the right anterior thigh has a mean very different from the left, it might be regarded as exceptional. Moreover, since the mean of the forehead is significantly greater than any of the 28 other sites, but is not significantly different from that of the right groin, it seems reasonable to define the groins, scalp and forehead as the most alkaline sites, with mean pH of 6.42 or more.

This analysis, as has been shown, will detect differences between site means as significant if they exceed 0.12. If the above seven points are reconsidered from the point of view of the clinical and aetiological importance of the differences observed, then those between sides of bilateral sites are relatively unimportant compared with those between flexor and extensor surfaces. The former never exceed 0.33 ± 0.06 whereas the latter range from 0.42 ± 0.06 to 0.81 ± 0.06 . In passing it should be noted that the flexor surfaces have higher means than the extensor surfaces which is the opposite of the conclusion reached by Blank (1939c) and whereas he found the antecubital fossa to be the most acid of the arm surfaces, we find it to be the most alkaline.

COMPARISON WITH OTHER PUBLISHED DATA.

Attention has already been drawn to the paucity of published data on children unaffected by skin disorders. Difficulties arise in comparing results of different investigators because of differences in technique, ages of subjects

studied and detail of reporting results. The data most comparable with ours are those of Anderson's (1951) normal subjects and Blank's (1939c) children, but some points need to be noted before such comparisons are made.

1. All three series were based on a glass electrode method of determination although in detail the apparatus was different.

2. Our subjects were younger (one to seven days) than Anderson's (one month to twelve years) and Blank's (three to fourteen years).

3. Our observations and Blank's were made on about 100 children of each sex and in each series each child contributed one determination to each site considered. Anderson's site means were never based on the complete series of her 50 children—the numbers on which her site means were calculated varied from 1 to 37.

4. Anderson gave her results for both sexes combined in the form of grouped frequency distributions for each site. Blank gave means and standard deviations for each sex and site separately.

In Tables V and VI, we have made the best use we can of these data by selecting sites common to our experiment and either or both of Anderson's and Blank's respectively. We have taken no account of any site tabulated by Anderson for which she had less than ten determinations.

Table V shows for Anderson's series the mean pH of six bilateral sites, without distinction between sides, and the scalp. These are compared with corresponding means from the present series which happen to be valid in the sense that no differences were found in our data to be significant between sides or between sexes for the sites in this table. The standard errors of the means of Anderson's series were derived from her frequency distributions. This may overstate the true standard errors because it is not clear from Anderson's report whether one or both sides of bilateral sites were included in the tables.

TABLE V.—*Comparisons of Mean pH (in pH units) Obtained in Present Series with that Reported by Anderson (1951).*

Site	Present series.		Anderson's series		Difference ±S.E. (a) - (b)	t	P
	N	Mean ± S.E. (a)	N	Mean ± S.E. (b)			
Dorsum of hand .	406	5.60 ± 0.03	37	5.04 ± 0.35	0.56 ± 0.36	1.56	0.20 > P > 0.10
Popliteal fossa .	406	5.91 ± 0.03	19	5.53 ± 0.48	0.38 ± 0.49	0.78	0.50 > P > 0.40
Wrist flexor .	406	5.95 ± 0.03	23	5.33 ± 0.42	0.62 ± 0.42	1.48	0.20 > P > 0.10
Palm .	406	6.13 ± 0.03	33	5.25 ± 0.36	0.88 ± 0.36	2.44	0.02 > P > 0.01
Cheek .	406	6.20 ± 0.03	22	5.28 ± 0.45	0.92 ± 0.45	2.04	0.05 > P > 0.02
Antecubital fossa .	406	6.33 ± 0.03	22	5.44 ± 0.36	0.89 ± 0.36	2.47	0.02 > P > 0.01
Scalp .	203	6.56 ± 0.04	10	5.00 ± 0.86	1.56 ± 0.86	1.81	0.10 > P > 0.05

N = Number of determinations on which mean is based.

S.E. = Standard error.

Table VI shows for Blank's series the mean pH for each sex separately for four bilateral sites, without distinction of side. The means are compared with

corresponding means from the present series. For three of these sites we have pooled our bilateral means because they were not significantly different; this was not true of the two upper arm extensor means which are consequently shown separately. The standard errors of Blank's means were derived from his published data on the standard deviations and numbers of determinations.

TABLE VI.—*Comparison of Mean pH (in pH units) Obtained in Present Series with that Reported by Blank (1939c).*

Site.	Present series.		Blank's series.		Difference ±S.E. (a) - (b).	t	P
	N.	Mean ± S.E.	N.	Mean ± S.E.			
		(a)		(b)			
<i>Boys</i>							
Elbow point . . .	200	5.60 ± 0.04	100	4.97 ± 0.05	0.63 ± 0.06	9.9	P < 0.001
Upper arm extensor L	100	5.75 ± 0.06	100	4.88 ± 0.05	0.87 ± 0.08	10.9	P < 0.001
Upper arm extensor R	100	5.65 ± 0.06			0.77 ± 0.08	10.0	P < 0.001
Upper arm flexor . .	200	6.26 ± 0.04	100	4.73 ± 0.04	1.49 ± 0.06	26.1	P < 0.001
Antecubital fossa . .	200	6.37 ± 0.04	100	4.62 ± 0.04	1.75 ± 0.06	30.7	P < 0.001
<i>Girls</i>							
Elbow point . . .	206	5.57 ± 0.04	100	5.11 ± 0.06	0.46 ± 0.07	6.4	P < 0.001
Upper arm extensor L	103	5.76 ± 0.06	100	5.16 ± 0.05	0.60 ± 0.08	7.7	P < 0.001
Upper arm extensor R	103	5.55 ± 0.06			0.39 ± 0.08	5.0	P < 0.001
Upper arm flexor . .	206	6.11 ± 0.04	100	4.97 ± 0.05	1.14 ± 0.06	17.8	P < 0.001
Antecubital fossa . .	206	6.29 ± 0.04	100	4.82 ± 0.05	1.47 ± 0.06	22.9	P < 0.001

N = Number of determinations on which mean is based.

S.E. = Standard error.

L = Left, R = Right.

The means obtained in the present experiment are consistently greater than those obtained by either Anderson or Blank. All the differences are significant except those for the dorsum of the hand, the popliteal fossa, the wrist flexor and the scalp with Anderson's data (Table V). Most of the significant differences are appreciable in size, ranging from 0.46 ± 0.07 to 1.75 ± 0.06 pH units.

Behrendt and Green (1958) had one site in common with us, the axilla, and they quote means and standard deviations. The means, with derived standard errors, are 6.3 ± 0.13 for infants aged under 48 hours, 5.0 ± 0.11 for ages 3 to 6 days and 4.7 ± 0.08 for ages 7 to 30 days. Our mean (both sides combined) for this site is 6.18 ± 0.03 which is not significantly different from theirs at ages under 48 hours, but very different at later ages which are similar to the ages of our subjects.

Thus, although the comparisons of Tables V and VI are of interest, it seems likely that many of the differences reflect differences in age between our subjects and those of Anderson and Blank. Thus what is of more interest is a comparison of relative sex and site differences observed by Blank from his data with corresponding differences observed by us from our data. On the five conclusions relative to children extracted from Blank's papers and listed earlier we can comment

1. Our range of pH determinations is much greater.
2. The dispersion of determinations in males and females is very similar in our data whereas Blank found greater variation among females than among males.
3. There is no sex difference in mean pH in our data whereas Blank found the mean for females to be greater than that for males.
4. Generally in our data, the flexor surfaces have a higher mean pH than the extensor surfaces whereas Blank found the reverse.
5. The antecubital area had the highest mean pH of all arm sites in our data whereas in Blank's it had the lowest.

Our findings appear to be in complete opposition to those of Blank in a number of important respects. It is hardly likely that relative differences between sub-group means within each experiment are likely to be influenced by difference in technique, so that the inference is that the whole pattern of the pH of the arm in infancy is different from that observed later in childhood. In this context an extension of the work of Behrendt and Green (1958) is obviously important since the comparisons imply that relationships between age and pH for extensor surfaces are different from those between age and the pH for flexor surfaces.

SUMMARY AND CONCLUSIONS.

1. Determinations of pH of the skin surface have been made at 34 body sites on each of 203 children (100 boys and 103 girls) aged 1 to 7 days. None had skin disease and the sample is believed to be representative of children of this age in this area.
2. The 6902 determinations were made by two observers in similar environmental conditions using a Marconi direct reading pH indicator. The accuracy of a determination was of the order of ± 0.2 pH units.
3. The design of the experiment was such that the minimum differences likely to be detected, between two sub-group means, as significant ($P < 0.05$) were 0.15 pH units between sex means for all sites combined, 0.23 pH units between sex means for a given site and 0.12 pH units between site means for both sexes combined.
4. For all sites combined, the sex means were not significantly different (6.12 and 6.04 pH units for boys and girls respectively). Only two sites, the left and right anterior thighs, had significantly different means for the sexes. The difference, 0.26 pH units, in each case was small enough to be ignored and on the criterion of significance used the apparent exception is not unexpected. We conclude that sex plays no important part in determining pH at these ages. This is not supported by work done elsewhere on older children in which mean pH for females was greater than that for males (Blank, 1939c).
5. Clinically important significant differences were found between site means.

Mean differences ranging from 0.42 ± 0.06 to 0.81 ± 0.06 pH units were found between corresponding flexor and extensor surfaces. The flexor surfaces consistently had the higher mean pH and this tendency was also observed in other pairs of adjacent sites. The reverse has been reported, by other workers, to be true for older children (Blank, 1939c).

6. On average the dorsum of the hands, the elbow points and the upper arm extensor surfaces were the most acid areas examined with mean pH of 5.75 ± 0.04 pH units or less.

7. On average the groins, scalp and forehead surfaces were the most alkaline areas examined with mean pH of 6.42 ± 0.04 pH units or more.

8. No comparable data exist for children of this age and the few comparisons possible suggest that the means in this series are higher than those reported for older children.

9. In view of differences in our paragraphs 4, 5 and 8 from the results of others working with older children, the work of Behrendt and Green (1958) appears to be very relevant. The changes in pH associated with age, which they reported for three sites, may be true of other areas and it may well be that the pH of flexor surfaces decreases more rapidly and to a lower level with age than does that of extensor surfaces.

10. Since there is indirect evidence that children with seborrhoeic disease have a more alkaline skin surface reaction over the whole body than other children (Anderson, 1951; Beare *et al.*, 1958) it might be possible to detect susceptible children long before illness develops. It is therefore important to have on record the distribution of pH levels as presented here, but it is equally important, in view of paragraph 9, that the associations of pH with age should be investigated more thoroughly.

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THE BEHAVIOUR OF RADIOACTIVE MERCURY AND ZINC AFTER APPLICATION TO NORMAL AND ABNORMAL SKIN.

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DURING investigations into the behaviour of externally applied radioactive sulphur, a specific pattern of distribution of the isotope was observed in two allied dermatoses, seborrhoeic dermatitis and psoriasis (Scott, 1957). This prompted a study of the behaviour of other cations—mercury and zinc—both of which behave chemically like sulphur and both of which have a successful but empirical use in the treatment of these dermatoses. In view of a possible association of sulphhydryl-containing amino acids with the distribution of radioactive sulphur, an attempt was made in this second investigation to relate the histochemical position of these SH groups to the autoradiographic localization of the cations under study. Finally, by affecting the activity of these groups we sought to demonstrate parallel alteration in the behaviour of the radioactive elements.

METHODS.

The patients studied included 49 normal controls, 42 with seborrhoeic dermatitis, 35 with psoriasis and 11 with subacute or chronic eczema. The lesions studied were all well defined and untreated at the time of the test. The two radioactive isotopes used were zinc (^{65}Zn) with a half-life of 245 days and mercury (^{203}Hg) with a half-life of 47 days. The radioactive zinc was supplied as zinc chloride and made up in an aqueous solution with stable zinc chloride as the carrier. One pipette drop of this solution had a radioactivity of 3.4 microcuries. Ammonium mercuric chloride in an emulsifying base served as the vehicle for the radioactive mercury, 50 mg. of the ointment delivering 5 microcuries of radiation. The radioactive material was applied to the skin after cleansing with ether, and massaged in with a glass applicator. A cellophane patch was then placed over the test site for four hours.

Contact Geiger counts were taken of the test area immediately after application of the radioactive material and again after its removal with ether four hours later. Readings of the protective cover were also taken. The values obtained permitted a calculation of the percentage of radioactive isotope retained in the skin.

The tested lesions were than biopsied after the final Geiger readings and sections submitted to autoradiographic examination using a method previously outlined (Scott, 1957). Serial sections were also treated histochemically using Chèvremont's stain for sulphhydryl-active groups.

The methods used to alter the local concentration of labile SH radicals may be divided into two groups. Those designed to inhibit their activity included ultra-violet irradiation in erythema-producing doses, Grenz irradiation in doses of 200r and vitamin A in oral doses of one million units daily in two cases and as a topical application of 100,000 I.U. per gram of ointment in the remainder. Methods used to increase sulphhydryl activity included the application of BAL (British Anti-

Lewisite) as a 5% ointment and Versene (calcium disodium ethylene diamine tetra-acetate) also as a 5% ointment. All applications were made twice daily for four days prior to the test.

RESULTS.

Zinc.

This element was found to be absorbed through the epidermis as well as through the entrances to hair follicles. Traces were found in the stratum corneum in autoradiographs taken within two hours of its application, while some had reached the dermis in four hours. At least 50% of the quantity applied to the skin was ultimately absorbed. Zinc showed a great affinity for all the living cells of the epidermis, concentrating on the internal aspect of the

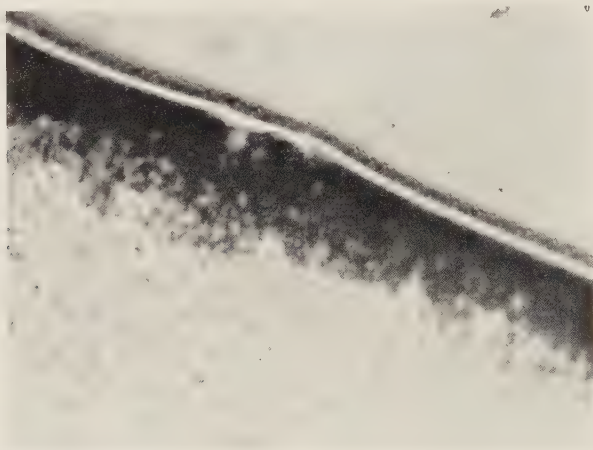


FIG. 1.—An autoradiograph of normal skin showing the dense epidermal retention of zinc (^{65}Zn). The tendency for zinc to be located peripherally in the cell may be observed by examination of the deeper layers of the epidermis.

cell membrane. No specific concentration was observed in any layer. Eczematous lesions usually showed a similar pattern of distribution of zinc, although in a few cases of lichen simplex, scattered intraepidermal clumping of the isotope within cells was noted. In the dermis, zinc aggregates were seen in histiocytes, endothelial cells and fibroblasts as well as some erythrocytes (Fig. 1).

Although in both seborrhoeic dermatitis and psoriasis, zinc eventually reached the dermis after 18 hours, in the former condition a concentrated band of zinc was demonstrated in the stratum granulosum, while in psoriasis it was heavily concentrated in the cells of all the layers of the epidermis. No greater quantity of zinc was held in the seborrhoeic lesion than in the normal, but the psoriatic patch retained nearly all the applied material. In both these conditions zinc was located intracellularly throughout the cytoplasm rather than at the cell periphery. In all the conditions studied, zinc was absorbed in

large quantities, but in seborrhoeic dermatitis and psoriasis these quantities were retained within the epidermis in specific zones for a long period (Fig. 2).

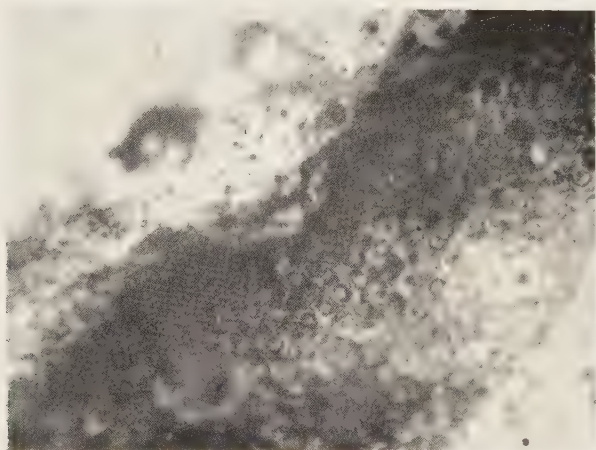


FIG. 2.—An autoradiograph of a psoriatic lesion, showing the distribution of zinc (^{65}Zn). The cells of the deep epidermis illustrate its tendency to be located around the nucleus rather than the periphery of the cell.

Mercury.

The route of absorption into the epidermis was the same as with zinc and the rate of percutaneous transfer was equally rapid. In the normal and eczematous skin about 10% and 15% respectively of the applied mercury were absorbed, but no particular area of retention was noted. The element passed diffusely through the epidermis and on reaching the dermis after 8 hours it was absorbed systemically. Examination of the autoradiographs revealed that the mercury was entirely extracellular in position, usually closely related to the intercellular

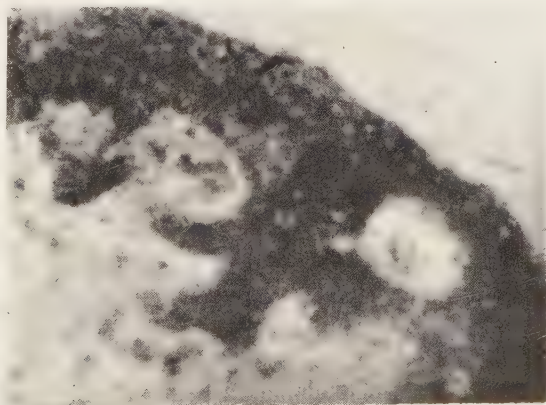


FIG. 3.—An autoradiograph of a psoriatic lesion, showing the distribution of mercury (^{203}Hg) throughout the epidermal layers.

bridges and the external surfaces of cell boundaries. Again it was observed that a few areas of a lichen simplex lesion often showed intracellular collections of mercury in the mid-epidermis. The lesions of seborrhoeic dermatitis and psoriasis retained a much higher proportion of the applied mercury, usually about 50% ; almost all of this accumulated in the stratum granulosum of the seborrhoeic patch, while in psoriasis it was evenly distributed through all the epidermal layers. In neither condition did the element reach the dermis. In contrast to the position seen in normal skin, the mercury in these lesions was entirely intracellular (Fig. 3).

These findings are summarized in Table I.

TABLE I.—*Comparison of the Behaviour of the Radioisotopes.*

Isotope	Diagnosis	Number of cases		Retained activity (mean %).	Localization		Cellular position.	Depth of penetration*
					Epidermis.	Dermis.		
Sulphur ³⁵ S	Normal	12	2		Non-specific		Extra-cellular	Dermis.
	Eczema	10	2		"	"	Ditto	"
	Seborrhoeic dermatitis	18	30		Stratum granulosum	None	Intra-cellular	Mid-epidermis
	Psoriasis	8	40		All layers	"	Ditto	Basal layer
Zinc ⁶⁵ Zn	Normal	21	80		Non-specific		"	Dermis
	Eczema	5	48		"	"	"	"
	Seborrhoeic dermatitis	20	52		Stratum granulosum	None	"	"
	Psoriasis	14	98		All layers	"	"	"
Mercury ²⁰³ Hg	Normal	28	10		Non-specific		Extra-cellular	"
	Eczema	6	15		"	"	Ditto	"
	Seborrhoeic dermatitis	21	50		Stratum granulosum	None	Intra-cellular	Mid-epidermis
	Psoriasis	21	46		All layers	"	Ditto	Basal layer

* If the radioisotope reached the dermis, it was systemically absorbed. Otherwise the isotope was transferred to the surface and discarded with normal desquamation.

HISTOCHEMICAL IDENTIFICATION OF SULPHYDRYL GROUPS.

A close parallel was noted between the deposition of radioactive mercury and sulphur in the autoradiographs and the position of free sulphydryl groups as identified by Chèvremont's stain. In the normal skin there was a diffuse extracellular distribution throughout the epidermis with concentrations around the cell membranes and intercellular bridges. In seborrhoeic dermatitis and psoriasis there was a dense stain in the mid-epidermis and in all the layers of epidermis respectively. In both these maladies the sulphydryl-staining material was intracellular.

ALTERATIONS IN THE NUMBER OF LABILE SULPHYDRYL GROUPS.

An attempt was made to decrease the number of labile SH groups by prior treatment of the tested areas with ultra-violet and Grenz irradiation and the

administration of pharmacological doses of vitamin A. Following the use of any of these agents, there was virtual disappearance of labile SH groups from biopsies of normal skin stained histochemically and autoradiographic examinations failed to show either absorption or retention of any of the radioactive isotopes after their external application to the treated site. The characteristic concentrations of stained sulphhydryl groups or of absorbed mercury or zinc failed to occur in seborrhoeic or psoriatic lesions which had been similarly treated prior to the tests. In both these dermatoses, the total quantity of absorbed radioactive material fell to approximately one-quarter of its former value. If the single treatment with external irradiation was insufficient to clear the lesion, the autoradiographic pattern tended to revert later to its former pattern. The administration of vitamin A either systemically or topically caused only a temporary reversion to a more normal pattern, but it was not continued long enough to attempt a clinical assessment of its final efficacy.

Little effect on the histochemical identification of SH groups resulted from the prior use of BAL or Versene in ointment form. However, in the normal skin a slight increase resulted in the quantity of sulphur, mercury and zinc absorbed, with a more dense concentration of these isotopes in the autoradiograph both intracellularly and extracellularly. In these cases, we were able to demonstrate mid-epidermal accumulation of mercury, resembling that seen in seborrhoeic dermatitis. Little change in isotope absorption was noted in seborrhoeic dermatitis or psoriasis, nor was there any alteration in their distribution (Table II). A tendency to separation of epidermal layers was noted in several of the treated lesions.

TABLE II.—*The Effects of Various Agents on the Behaviour of Mercury.*

Test gent.	Percentage of mercury (^{203}Hg) retained in skin lesion (mean value).				Specific localization in autoradiograph.	
	Normal.		Psoriasis.		Normal.	Psoriasis.
	Before.	After.	Before.	After.		
Ultraviolet rays . . .	10	Nil	46	10	None	None
Grenz rays	10	2	46	Nil	"	"
Vitamin A (ointment) . .	10	4	46	8	"	"
Versene (ointment) . . .	10	22	46	50	Mid-epidermal	All layers
BAL (ointment)	10	18	46	50	Ditto	Ditto

Two additional conditions were studied because of the possible implication of abnormalities in sulphhydryl groups in their pathogenesis. Two patients with pityriasis rubra pilaris were examined by means of biopsies at intervals during therapy with vitamin A. The period of observation occupied about eighteen months until their lesions disappeared and treatment was stopped. A gradual decline was noted in the total quantity of radioactive sulphur and mercury absorbed into the epidermis, from initial values of 30% to final levels

of 6%. The autoradiographic pattern showed an initial diffuse intracellular epidermal distribution resembling that seen in psoriasis, and an extracellular concentration as seen in normal skin, after the lesion had resolved. It is interesting that similar alterations in isotope pattern were demonstrable in the seemingly normal epidermis between typical lesions. Four patients with vitiligo were examined as well. Fifty percent of the applied mercury was absorbed, epidermal retention was brief (2 hours), but the radioactive material was located intracellularly during this time with a particularly dense deposit in the basal layer.

DISCUSSION.

In the human epidermis, the process of keratinization involves the reorganization of the sulphydryl groups of the amino acids cysteine and methionine into the disulphide linkages of cystine. These latter groups appear to serve as cross-linkages in the α -keratin molecule, providing much of its stability and resiliency (Rudall, 1952). In the case of cysteine, the process of alteration is relatively simple since the SH group in question is free or labile because of its position at the end of the molecule. These groups are by consequence also water-extractable. However, the conversion of methionine is more indirect since the sulphur ion is separated from the end of the molecule by a methyl group; hence simple oxidation would produce methylsulphonic acid. It seems that methionine must undergo a process of transmethylation with either serine or choline before the sulphydryl group becomes reactive. This transmethylation in the skin probably is catalyzed by cyanocobalamin and by folic acid, both of which serve as catalysts in this conversion in the liver. The result is homocysteine, which in company with cysteine, is irreversibly oxidized, via an intermediate hydrolysis, to cystine, the disulphide-containing amino acid of keratin. Since the keratin of the stratum corneum still contains some methionine, although in a smaller proportion than in the basal layer, it is obvious that there is not a complete conversion. This process may be traced to some extent histochemically, since there has been shown to be a high concentration of SH groups in the basal layer (presumably those of cysteine) which becomes progressively less as the surface is neared (Montagna, 1954). However in the stratum granulosum there has been identified a broad SH band—the so-called “keratogenous zone” of Giroud—where there is a sudden increase in the proportion of SH radicals in labile form before final conversion takes place. It is theoretically possible that it is at this point that the demethylation of methionine has rendered free the SH groups of that amino acid which are then able to react with the histochemical reagents used for their detection.

As Montagna and his group have shown, the various SH stains demonstrate the presence of these groups in normal skin sections within the tonofibrils and intercellular bridges of the basal and prickle-cell layers, suggesting that these structures are the fore-runners of keratin bodies. In our studies of the behaviour

of both radioactive mercury and sulphur, autoradiography showed the extracellular position of these elements particularly in the intercellular bridges of the normal skin. Such an observation strengthens the belief that these bridges contain a concentration of labile SH groups possibly in the form of cysteine. Since both these isotopes were also seen to be deposited around the cell boundaries, it would appear that these regions retain their SH reactivity longer than the remainder of the cell. There was no specific localization of the isotopes in the various epidermal layers. The relatively low percentage of the elements retained in the epidermis—10%—suggests that although there are some labile SH groups available in the normal skin, most of these radicals are in the bound, non-reactive form. It is not yet certain whether this state indicates a deep infolding of the protein molecule so that the SH groups are not available for any reaction.

Irradiation oxidizes the SH radicals exposed to it and vitamin A accomplishes the same conversion by virtue of the presence of an unsaturated double-bond in its structure (Flesch, 1952). Both reduced the total quantity of radioisotopes absorbed almost to nil. The use of the two chemicals BAL and Versene was designed to increase the number of available SH groups by displacing any attached ions. Their administration did not materially alter the quantity of radioisotope absorbed, but autoradiographs revealed small intracellular concentrations of the elements, particularly in the stratum granulosum. In other words, the autoradiographs assumed to some extent the appearance seen in the true seborrhoeic lesion, although for a few hours only. Our inability to alter the total number of reactive SH groups suggests that the proportion of these radicals proceeding along a path of direct oxidation to disulphide linkages is relatively constant, involving the smaller percentage of the total number of SH groups present in the normal skin. The chelating agents, however, can at least temporarily slow the process of final conversion, so that freed SH groups may be visualized in the mid-epidermis.

Examination of the behaviour of radioactive zinc demonstrated some differences which would seem capable of explanation on the basis of its many known functions, primarily as a catalyst in intracellular enzyme systems involving hexokinase and tyrosinase. The most obvious difference lay in the high proportion of zinc absorbed—up to 100% in some normal skins. Secondly, the element was located intracellularly as well as extracellularly in the autoradiograph, further supporting the conception of zinc as a natural catalyst in various intracellular reactions.

Relatively little is known about the process of pathological keratinization seen in psoriasis, seborrhoeic dermatitis and lichen simplex. Magnus (1956) has demonstrated in quantitative studies a high value for the freely available SH groups in homogenates made from lesions of these dermatoses, while Braun-Falco (1956) has shown a high proportion of methionine in the scales

from psoriasis at least. Several facts emerge from our studies which may throw some light upon the abnormal processes seen here. Both seborrhoeic dermatitis and psoriasis are characterized by an increased retention of all the radioisotopes. The absorption may be as high as four times normal. Both lesions have a characteristic distribution of the isotopes. In seborrhoeic dermatitis, the elements are densely deposited through a band in the stratum granulosum, while in psoriasis the elements are densely distributed throughout all the epidermal layers. Especially in the cases of sulphur and mercury, there is a change to an intracellular position; zinc, already intracellular, does not alter. Where parakeratosis has been identified histologically with routine stains, the above features are most predominant. They may also be seen in chronic lichen simplex. Methods which tend to decrease the concentration of SH groups are associated with a decrease in the absorption of the radioisotopes, a temporary or permanent reversion of their distribution pattern to normal and may be accompanied by or cause a clinical amelioration of the lesion. The use of methods which increased the proportion of reactive SH groups fails to alter the picture of radioisotope behaviour and may aggravate the clinical lesion. On the other hand, these agents may produce the temporary autoradiographic picture of a seborrhoeic lesion when they are used in normal skin.

These observations suggest a close connection between the number of available reactive SH groups and the state of the pathological lesion. One of the primary faults in both seborrhoeic dermatitis and psoriasis is an abnormality in the process of keratinization, giving rise to what is termed parakeratosis. Since there is no marked disparity in the total amino acid sulphur content of these lesions and that of normal skin, the likelihood is that the basic lesion originates from a block in the conversion of sulphydryl to disulphide linkages, with or without a simultaneous refolding of the fibrous structures. In view of the temporary production of the autoradiographic pattern of seborrhoeic dermatitis by the use of chelating agents, it is possible that the block develops from a failure in a metallic ion serving as a catalyst in the keratinization process. Successful although temporary treatment of these lesions results from the acceleration of the keratinization process by irradiation, which through the inhibition of SH-group activity serves to complete the normal process. Stable mercury, sulphur and zinc are also successful therapeutic agents. Since the radioisotopes behave chemically in the same fashion as their stable counterparts, the latter would seem to effect clinical improvement through alteration in SH-reactivity by absorption of the cation on to the SH-containing amino acid. Their presence appears to hasten keratinization along the normal pathway.

SUMMARY.

The radioisotopes mercury (^{203}Hg) and zinc (^{65}Zn) were utilized to study the behaviour of these elements when applied to normal skin and to lesions of

chronic eczema, seborrhoeic dermatitis and psoriasis. Geiger readings and autoradiography were used to trace the isotopes and tissue was also stained histochemically for sulphhydryl groups.

A high proportion of radiozinc was absorbed and retained in all cases. Autoradiography showed that it was always intracellular, but tended to be situated peripherally in normal skin and centrally in the epidermis of seborrhoeic and psoriatic lesions. A specific localization in layers was noted in the latter two conditions. Radioactive mercury closely paralleled the behaviour of sulphur (^{35}S). Only 10% was retained in normal and eczematous skin, while seborrhoeic and psoriatic lesions retained 40–50%. Intracellular autoradiographic localization was observed in these two conditions as well as the same specific distribution in layers encountered with radiozinc.

A close relationship was noted between the autoradiographic patterns obtained and histochemically localized sulphhydryl groups.

Attempts to affect the activity of available SH groups resulted in parallel alterations in the histochemical and autoradiographic pictures. The most notable of these changes was the temporary production of mid-epidermal concentration of radioisotopes in the normal skin after the use of either Versene or BAL ointments.

After a review of the current theory of keratinization, several facts established by the above studies are used to suggest a relationship between abnormal keratinization and the pathogenesis of both seborrhoeic dermatitis and psoriasis. An explanation of the usefulness of various methods of therapy in these dermatoses is advanced.

I thank Dr. R. M. B. MacKenna for his interest, and Professor T. Rotblat, Department of Physics, St. Bartholomew's Hospital Medical School, and his physicist, Miss A. MacAlister, for assistance. The radioactive isotopes were obtained through the courtesy of the Atomic Research Establishment, Harwell.

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PYODERMA GANGRENOSUM WITH CLUMPING OF BLOOD CELLS AND ABNORMAL PLASMA PROTEIN.

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PYODERMA gangrenosum is uncommon but well recognized. The purpose of this paper is to report a case without associated disease in which investigation showed curious clumping of the blood cells and an abnormal plasma protein.

CASE REPORT.

A male market gardener aged 57 was first seen in 1954, when he had had recurrent pea-sized "blind boils" for three to four years and large ulcers for six months. He had not suffered from diarrhoea and there was nothing of note in the past or family history. Examination showed lesions of pyoderma gangrenosum in all stages, scattered over most of the body and limbs. From 1954 until the present, his condition has fluctuated in severity but he has never been without lesions. The stools have remained normal. Treatment with various antibiotics did not appear to affect the condition; cortisone administration coincided with improvement, but relapse occurred whilst he was on the same dose.

General investigations.—The urine, blood Wasserman and Kahn reactions, skiagram of chest and repeated examinations of the stools for occult blood showed no abnormality. E.S.R. (Wintrobe) 23 and 41 mm./hr. (P.C.V. 38 and 47%). The haemoglobin varied between 14.8 and 8 g. per 100 ml. (the latter figure occurred after the period of most extensive ulceration which caused persistent blood loss). Serum proteins 6.5 g. per 100 ml. (albumin 4.0 g., globulin 2.5 g.). Numerous cultures and direct smears from the lesions demonstrated varied flora, strains of *Staphylococcus aureus* being predominant. Biopsies from new lesions and from the base of an established ulcer showed abscesses and granulation tissue infiltrated by neutrophil and eosinophil leucocytes.

Serological investigations.—On attempting blood leucocyte counts it was noticed that the cells clumped in the counting chamber, rendering the count difficult or impossible. This phenomenon fluctuated in degree but was noted at intervals from 1955 to 1958. It was present in both oxalated venous blood and capillary blood samples. The method used in these leucocyte counts was to take 0.2 ml. blood into 1.8 ml. diluent (0.025 g. malachite green, 1 ml. glacial acetic acid, 100 ml. distilled water) shake for 3 minutes and fill a Fuchs-Rosenthal counting chamber which was kept in a moist chamber at room temperature and examined after a few minutes. The appearance in the counting chamber suggested that the leucocytes became clumped because they were

enmeshed in strongly agglutinated masses of red cell stromata. In minor degrees, agglutination of red cell stromata is common with blood from other patients but it does not interfere with leucocyte counting. By mixing cell-free plasma from the patient with normal oxalated whole blood, it was shown that the agglutination was caused by the patient's plasma. Six samples of normal plasma did not possess this property. It appeared to be dependent on the presence of 0.5-1.0% acetic acid in the diluting fluid, and was absent when the acetic acid was omitted or increased to 2%.

Fractionation of the patient's plasma with saturated ammonium sulphate suggested that the acid-dependent agglutinating activity lay in the fraction deposited at 50% saturation, there being less marked activity in the fractions precipitated by full saturation and by 40% and lower concentrations. Storage of the patient's serum and plasma at 4° C for several days resulted in a small deposit in the latter. It was partly soluble at 37° C, reappearing again at 4° C. Waldenström's test for macroglobulinæmia was negative. Extensive tests for red cell auto-antibodies were negative. The cold-agglutinin titre in saline was 1 : 4 at 4° C. The patient's plasma failed to agglutinate leucocytes in normal leucocyte-rich plasma at room temperature. These findings suggested the presence of an unusual protein component in the patient's plasma, which by physical effects caused an increase of red cell stromal agglutination.

In order to elucidate the nature of the abnormal protein, separations of the plasma and serum were performed by paper electrophoresis. On two occasions there was present in the serum an extra band between the expected β - and γ -globulin fractions. Examination of oxalated plasma on one occasion showed a similar phenomenon. The relative percentages of this abnormal fraction on the three separations were 10.87% (serum), 6.97% (serum), and 7.06% (plasma) of the total protein. The specimens were centrifuged at 0° C and the opaque layer removed. This fraction, which behaved like a cryoglobulin, had an electrophoretic mobility greater than that of γ_1 -globulin and slightly less than that of a β_2 -globulin. After elution from an unfixed paper strip, the protein was hydrolyzed with 6N HCl. The hydrochloric acid was removed *in vacuo*, the solution isolated by chromatography and the presence of hydroxyproline demonstrated. The presence of this particular amino-acid may be considered to differentiate a cryoglobulin from macroglobulin, γ -globulin, Bence-Jones protein and the pyroglobulins (Huisman *et al.*, 1956). The ultraviolet spectral absorption of the isolated protein was not established.

DISCUSSION.

Such serological findings do not appear to have been recorded with pyoderma gangrenosum and their occurrence in this patient may represent a chance association. On the other hand, if they are looked for specifically it is possible that further similar findings will come to light.

It is difficult to know if the abnormality of plasma proteins and the cell clumping play any part in the aetiology of pyoderma gangrenosum. The lesions do not appear to be infective in origin and Percival (1956) has reported a case associated with ulcerative colitis in which the initial skin lesion consisted of epidermal necrosis. This resulted in the formation of bullae, the contents of which were sterile. There may be some immunological or biochemical cause related to our findings.

Marcussen (1955) described a case of pyoderma gangrenosum without associated disease in which γ -globulin was consistently much diminished or absent. It is difficult to believe that an immune mechanism could have caused the disease in such a case. Rostenberg (1953) suggested that cases of pyoderma gangrenosum complicating ulcerative colitis might be manifestations of a dermal Schwartzman phenomenon following absorption of bacterial substances into the blood stream. In the experimental animal, injection of the substance provoking a Schwartzman phenomenon is associated with decrease in numbers of granulocytes and platelets in the blood and clumping of these cells in the lungs and particularly in the prepared skin site (Stetson, 1951).

SUMMARY.

In a case of pyoderma gangrenosum without associated disease, clumping of cells was noted during routine leucocyte counts. It was probably due to a cryoglobulin in the patient's plasma.

The patient is under the care of Dr. R. Bowers and we are very grateful for his help and encouragement. We would also like to thank Professor C. Bruce Perry, Dr. C. D. Evans and Dr. G. K. McGowan for their advice in preparing the paper.

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HAEMANGIOSARCOMA.

A CASE REPORT.

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HAEMANGIOSARCOMA (malignant haemangioendothelioma or haemangio-blastoma) is very rare and few large series of cases have been published. "In order to identify a malignant tumour as truly angiomatous there must be clear microscopical evidence of its essentially vaso-formative character and this is not easy to adduce" (Willis, 1950). On the other hand, an undoubtedly malignant lesion may be present clinically, but the pathological specimen may not show the true character of the condition and may display the picture of a benign angioma (Bormann, 1907). An extremely vascular sarcoma may be confused with a primary angiosarcoma. The following case report demonstrates the difficulty of confirming a diagnosis.

CASE REPORT.

A man aged 73 was referred to the Radium Institute. Three months previously he had noticed a painful itchy patch of discoloration in the left temporal region, which rapidly spread on to his scalp. Examination revealed a healthy looking man. There was a diffuse purplish area in the left temporal region and adjacent scalp, measuring 100 sq. cm. It was raised above the surface, hot to the touch and slightly tender. The lesion resembled a cavernous haemangioma but the surrounding induration suggested malignancy.

A biopsy specimen was reported to show a haemangioma. No treatment was given. However, the lesion extended rapidly and bleeding occurred, necessitating ligation of the left external carotid artery. Two weeks after, further haemorrhage took place and to prevent bleeding a single dose of 750 r of X-rays at 250 KV was given to the involved area. Two days later, the patient collapsed with signs of internal bleeding. There was evidence of fluid in both pleural cavities and a diagnosis of bilateral haemothorax was made. He died shortly after.

POST-MORTEM EXAMINATION.

Over an extensive area involving the left side of the face and scalp and spreading over the right side of the latter there was a superficial tumour infiltrating the skin giving it the purplish appearance of a haemangioma (Fig. 1). The tumour was extensively ulcerated in the scalp. It had not extended more deeply than the deeper dermis and stripped easily from the underlying skull which was not invaded.

Pleural cavity.—Free blood was present in both cavities. Extensive areas of both parietal and visceral pleura were replaced by superficial areas of haemorrhage which appeared to be associated with infiltration of tumour.

Lungs.—The lungs were collapsed and both were diffusely infiltrated by small firm nodules.

Liver.—Superficial subcapsular areas of haemorrhage on the anterior aspect of the left lobe and a few small tumour nodules within the liver substance. Small superficial haemorrhagic foci were present over the mesenteric surface.

Kidneys.—Normal size. Areas of subcapsular haemorrhage similar to those in the liver were present on the right kidney.



FIG. 1.

Microscopy. Sections of scalp, pleura, lungs, mesentery, liver, kidneys, suprarenals and pituitary were submitted for examination. The sections from the scalp showed the upper corium infiltrated with a vascular tumour which appeared in parts to be forming new vessels, and in others to be invading and growing freely within the lumen of pre-existing channels (Fig. 2). The malignant cells showed considerable pleomorphism, varying between flattened spindle cells lining vascular spaces and sheets of cells, some epithelial-like and others large multinucleated giant cells which were either infiltrating the dermis or growing apparently freely within dilated capillary channels. Areas of necrosis and acute inflammatory reaction, possibly due to occlusion of vessels by tumour, were present. The epithelium showed hyperkeratosis, keratotic plugging, bullous oedema and also direct infiltration with tumour resulting in ulceration and acute inflammation in the underlying tissues. The metastatic deposits in the pleura, liver, lungs and mesentery showed essentially similar appearances to the skin except that haemorrhage was a much more pronounced feature.

The appearance of these tumours seemed to be that of the group of malignant haemangioendothelioma, but it was impossible to exclude an anaplastic carcinoma invading blood vessels.

DISCUSSION.

Haemangiosarcoma is usually localized, bulky and deeply situated. It invades fat and muscle but not bone or tendon. Necrosis, haemorrhagic cyst-like cavities and mucoid degeneration are common (McCarthy, 1950). Spread

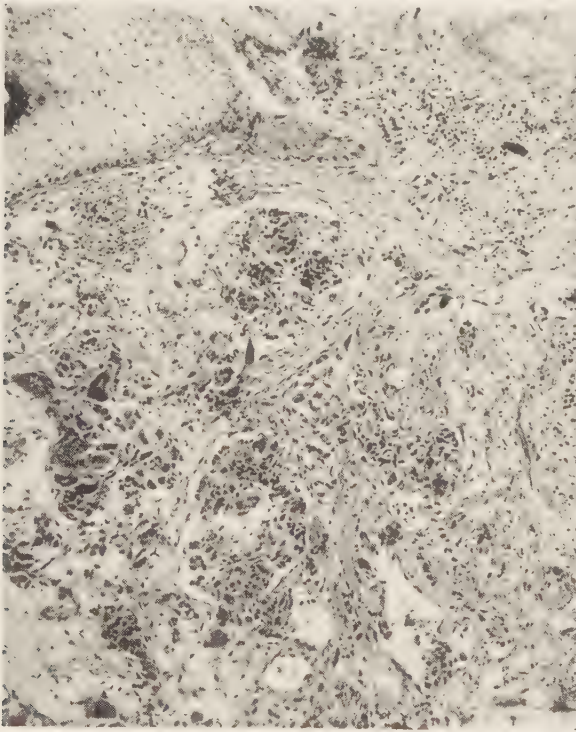


FIG. 2.

by the blood stream and lymphatics occurs to distant organs (Raven, 1954). The disease is almost invariably fatal, only 9% of cases surviving 5 years. For a more detailed discussion on the subject, I refer readers to the papers of Kinkade (1949) and McCarthy and Pack (1950).

In spite of teaching to the contrary, benign angiomas may become sarcomatous; but this must be extremely rare when one considers the frequency of angiomas. Raven (1954) described the development of an angiosarcoma in a haemangioma present since birth on the arm of a woman aged 61. McCarthy (1950) described three cases which had been irradiated and developed malignancy 4, 12 and 15 years afterwards. The first two patients had also

been treated by surgical excision. In recent years a new entity has been described viz., angiosarcoma occurring in chronically oedematous arms after mastectomy (Stewart and Treves, 1948). It is probably true to say that the condition is not new but that its recognition is recent. It escaped true diagnosis in the past and it was considered to be a metastasis from a breast carcinoma. Radical surgery in the form of amputation may be curative in these cases (McConnell, 1958).

SUMMARY.

A case report of a malignant blood vascular tumour and a short review of the literature on the subject are presented.

I wish to thank Dr. J. S. Fulton, Medical Director, for permission to publish this case and Dr. E. M. McConnell for the description of the pathology.

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BOOK REVIEWS.

"ROXBURGH."*

THIS is the first edition of "Roxburgh" since the death of the founder in December 1954 and it is a happy thought to alter the original title to "Roxburgh's Common Skin Diseases". That this book fulfilled its original aim to provide a book on common diseases described from the point of view of diagnosis and such treatment as the general practitioner can give is shown by the fact that there have been eleven editions since 1932. This new edition by Peter Borrie (himself also Cambridge and Bart's) is ably carrying on the same tradition and the future of "Roxburgh" is in safe hands. A book which has gone through so many editions in such a short time has been subject to so much revision and polishing that any adverse criticism must of necessity be small and based on purely personal views. For instance I would like a clearer exposition of the dermatitis-eczema relationship. This is not expressed clearly in this book and yet it is a subject which medical students and general practitioners always find confusing and difficult. The extensive use of superficial X-ray therapy is reminiscent of the older dermatology; few of the present dermatologists would, I believe, treat a corn by X-ray giving 400 r, or, I think, would be happy to give a further epilating dose after unsuccessful epilation of the scalp even after an interval of three months.

The early chapters on diagnosis and general treatment are good with the very proper emphasis on treating the patient and not the disease. More guidance could have been given in elucidating the cause of the stress in the treatment of lichen simplex since success in treatment depends entirely on this. But these are small points and only serve to emphasize the high standard of the book. The balance of space given to the different diseases is right, the treatment is sensible and the illustrations are very good. Objection is sometimes raised to black and white illustrations but these show beautifully the characteristics of the lesions and many of us are realizing now that we are seeing dermatoses in pigmented skin, that too much reliance can be placed on colour for making a diagnosis.

This latest edition would have pleased the original author.

H. R. V.

THE FRENCH ENCYCLOPAEDIA.†

COLLECTION No. 49-50 contains articles on various aspects of cancer and some subsidiary notes on syphilis. Of immediate interest to the dermatologist is a concise account of the treatment of cancer of the skin. No. 53 has major articles on "erythèmes polymorphes", dermatomyositis, lupus erythematosus and lichenification. The first term has a wider implication than the English erythema multiforme and includes eruptions secondary to drugs and infections though the possible aetiology of the idiopathic type is discussed. All four accounts are up to date, with good illustrations, and well documented, though there is no reference to Hobbs' and Calnan's work on the eye complications of chloroquine. Other subjects briefly dealt with include views on acne, reticulo-histiocytoma, chelators and congenital dyskeratosis associated with myelopathy.

F. F. H.

* *Roxburgh's Common Skin Diseases*. Eleventh Edition (1959). Revised by P. F. BORRIE. London: H. K. Lewis & Co. Pp. 496, 223 illustrations. Price £1 17s. 6d.

† *Encyclopédie Médico-Chirurgicale*, Periodic Collections No. 49-50 and No. 53. Paris: Éditions Techniques.

SKIN TUMOURS.*

THIS book deals with the clinical and histological diagnosis and treatment of "tumours" of the skin. It represents a list of lumps of different origin and its aim is apparently to give a busy practising dermatologist quick information about skin conditions representing both true and "false" tumours. The book is well written and the illustrations of high standard. The references are up to date and the German easy to read.

H. H.

DERMATOLOGIE UND VENEROLOGIE.†

THE second volume of this new German handbook has appeared recently. It consists of two parts; the first deals with physical treatment, dermatological cosmetics and diseases of unknown aetiology, the second with further diseases of unknown cause and diseases of known origin. This work is a valuable contribution to dermatological literature. Paper and printing are very good. The first part contains a very excellent section on special x-ray therapy by Proppe and there are valuable chapters on high speed electrons and radioactive isotopes. The section on dermatological cosmetics contains much useful information about a great variety of cosmetic agents, such as powders, hair lotions, lip sticks, nail varnishes, cosmetic creams and tooth-pastes. In the second part the chapters on parasitic dermatoses and mycoses deserve special mention for their excellence. The chapter on acute bacillary diseases and zoonoses gives very good accounts of such rare conditions as erysipeloid, anthrax, skin brucellosis, tularaemia, glanders, toxoplasmosis and rat bite fever. The quality of illustrations is on the whole very high, but a few are unfortunately below standard and in some chapters more illustrations would have enhanced the value of the text.

W. G. T.

COLLAGEN DISEASES.‡

THIS is a paper-backed edition, being the first of three volumes reporting the French Congress held in Paris in 1957. There are three comparatively short presentations—an introduction, dermatological aspects of collagen diseases, and rheumatic aspects of collagen diseases. There are also two longer and more valuable ones—a comprehensive revue of the biology and pathology of collagen, by Delaunay and Bazin, and also a good account of the visceral manifestations of the various collagen diseases by Turiaf, Marland, and Moreau. Both of these latter articles present a fund of information.

As is usual with such symposia, there is a considerable overlap between these papers, and there is nothing particularly original or startling in any of them. It is refreshing to read the following statement: "We regret the title of collagen disease; one cannot speak of a disease of a particular protein. Rather should we use a phrase 'connective tissue disease'"—a concept with which the majority are in accord.

S. C. G.

* *Die Geschwuelste der Haut*. ALOYS GREITHER and HELLMUT TRITSCH (1957). 180 illustrations. Stuttgart: Georg Thieme Verlag.

† Edited by PROFESSOR H. A. GOTTRON, Director of the University Skin Clinic, Tübingen, and PROFESSOR W. SCHÖNFELD, Director of the University Skin Clinic, Heidelberg. Stuttgart: Georg Thieme. Price of Volume II: DM 327.—(If all volumes are ordered: DM 261.60.)

‡ *Les Collagenoses* (1957). Paris: Masson & Co.

CURRENT LITERATURE.

ISOLATION OF HERPES-SIMPLEX VIRUS FROM A PATIENT WITH ERYTHEMA MULTI-FORME EXUDATIVUM (STEVENS-JOHNSON SYNDROME). D. W. FOERSTER and L. L. SCOTT. (1958) *New Engl. J. Med.*, **259**, 473.

Isolation of the virus of herpes simplex from vesicular fluid in a patient with erythema multi-forme exudativum is described. A. D. P.

PROLONGED URTICARIA AFTER INGESTION OF SULFAMETHOXYPYRIDAZINE. Capt. B. M. BELL, Capt. G. V. VIORES and Capt. W. E. FURST. (1958) *New Engl. J. Med.*, **259**, 585.

Urticaria which appeared after a man had taken a single tablet of sulfamethoxypyridazine lasted 17 weeks. The urticaria was thought to be due to sensitivity to the drug. A. D. P.

ORAL TREATMENT OF KELOIDS. EDWARD W. KELLY, jnr. and HERMAN PINKUS. (1958) *A.M.A. Arch. Derm.*, **78**, 348.

This article gives the result of 5 years experience in treating keloids with oral administration of tetrahydroxyquinone (THQ). Doses varied from 30 to 180 mg. daily. There were no ill-effects. There was some favourable influence in every case but recent cases respond better than those of long standing. The treatment is tedious and slow in action and its effect is incomplete in large keloids but it relieves the commonly associated pain and pruritus "rather promptly". J. K.

A STUDY OF CERTAIN CONTRIBUTORY FACTORS IN THE DEVELOPMENT OF VITILIGO IN SOUTH INDIAN PATIENTS. MARIAN LEVAL. (1958) *A.M.A. Arch. Derm.*, **78**, 364.

The author has studied 410 cases of vitiligo seen over a period of 3 years. The following factors appeared to influence its incidence: the higher level of ovarian hormones in women over 20 may provide a protective influence against depigmentation but this is lost after the menopause; nutritional deficiency especially of vitamin B contributes to the development of vitiligo but a low ascorbic acid level may prevent clinical depigmentation; other factors such as heredity, toxic causes, an allergic diathesis and psychogenic factors are less obvious but may contribute to its occurrence. J. K.

THE RELATIONSHIP OF PRURITUS AND LOCAL SKIN CONDITIONS TO THE DEVELOPMENT OF VITILIGO. MARIAN LEVAL. (1958) *A.M.A. Arch. Derm.*, **78**, 372.

Of 253 patients with vitiligo 44% gave a history of antecedent skin disease in an area of depigmentation, 10% complained of itching without clinical lesions and 15% had depigmentation in areas of pressure or irritation.

Noradrenalin is carried by sympathetic nerves to the spleen and if its precursor, DOPA, is likewise carried by sympathetic nerves to the skin, interference with its passage by perineural and perivascular inflammation may result in a decrease in the amount of DOPA reaching the skin and consequent depigmentation. Response to treatment with psoralen drugs may be a little slower in vitiligo patients who give a history of prior skin disease or irritation than in those without these factors. J. K.

THE PSEUDO-PELADIC STATE: CONSIDERATIONS OF LICHEN PLANUS OF THE SCALP. R. DEGOS, R. RABUT and P. LEFORT. (1957) *Arch. belg. Derm. Syph.*, **13**, 285.

Study of a further 109 cases have confirmed the authors in their view that there is no "pseudo-pelade" but a "pseudo-peladic state" which may be secondary to diseases recognized clinically or histologically as lupus erythematosus, lichen planus, lichen spinulosus, keratosis follicularis, scleroderma or folliculitis decalvans. Where no such disease is found it may have been present years before or appear subsequently.

Lichen planus of the scalp is not common, it is liable to be confused with ill-defined follicular keratoses such as keratosis pilaris and lichen spinulosus. Lichen planus of the scalp most frequently results in the appearance of one form of pseudo-pelade. J. K.

DIFFUSE SCLERODERMA : A CLINICAL STUDY OF SIXTY-FIVE CASES. Z. ŠTÁVA. (1958) *Dermatologica*, 117, 135.

A searching analysis of this large group brought out a number of facts. Diffuse scleroderma of the acrosclerotic type seems to affect women only, and to be closely related to sex-determining factors. Diffuse generalized scleroderma, on the other hand, affects both sexes equally. When, as is most common, acrosclerosis begins with Raynaud's phenomenon, the age of onset lies between 20 and 30, but when the sclerodermatous changes are present from the outset, the onset lies between 30 and 50. Acrosclerosis is associated with the sexual activity of women. In 30% of cases there is either an early menopause or marked disturbance of menstruation. In 15% it either starts at the menopause, or the latter is accompanied by an exacerbation. Almost a third of the married patients are childless, and a further third have one child only. Heredity could not be implicated. Progressive rheumatoid polyarthritis and Sjögren's syndrome were the most frequently associated conditions. Although visceral involvement cannot always be diagnosed clinically, and then usually only in oesophagus and lungs, it is probably usual in advanced acrosclerosis. Involvement of heart, endocrine glands and central nervous system are usually impossible to detect clinically, but increased sympathetic excitability is an almost constant finding. No impairment of liver or kidney function could be detected, and blood counts were normal. Raised B.S.R. and dysproteinaemia were in close relationship with the progress of the acrosclerosis. The extent and degree of visceral involvement do not run parallel to the degree of skin involvement. J. F. S.

SERUM PROTEINS IN SCLERODERMA. Z. ŠTÁVA. (1958) *Dermatologica*, 117, 147.

This study includes 100 analyses on 46 patients with diffuse scleroderma of acrosclerotic or diffuse generalized type and 45 analyses on 26 patients with circumscribed scleroderma, and is thus on an unusually large scale, compared to other reports in the literature. The results show a rise in gamma globulins, parallel to the degree of involvement of the skin or viscera, but less in diffuse generalized scleroderma and circumscribed scleroderma than in acrosclerosis, even when in the first-named the skin involvement was very extensive. As diffuse generalized scleroderma was fatal in from 5 months to 4 years, the much longer duration of acrosclerosis may have had something to do with this finding. On the other hand, two cases given the rather paradoxical name of generalized circumscribed scleroderma have shown high levels of gamma globulin, and the level has been rising progressively, parallel to the worsening of the skin condition. A rise of gamma globulin parallels the progression of the disease both where visceral involvement can be proved and where this is at most doubtful, and it probably depends chiefly on the degree of skin involvement. The author does not consider that his findings support the view that scleroderma falls into the group of the so-called collagen diseases. The fact that the dysproteinaemia is uninfluenced by ACTH or cortisone is against the theory that there is an immunobiological mechanism in the pathogenesis of these diseases. J. F. S.

THE EFFECT OF INOCULATION WITH B.C.G. ON DINITROCHLORBENZOL ECZEMA IN THE GUINEA-PIG. J. R. FREY and P. WENK. (1958) *Dermatologica*, 117, 154.

Earlier work by the same authors has shown that the regional lymph-nodes are the sites that manufacture the substance(s) responsible for skin sensitization against dinitrochlorbenzol in the guinea-pig. Their present study brings out that inoculation of B.C.G. and application of DNCB carried out simultaneously and at the same site, result in a potentiation of sensitization, but that if the two procedures are applied at different sites, no such potentiation takes place. Since contact eczema is believed to depend on the development of specific antibodies, and an increase in these antibodies must be assumed as a basis for potentiation, it is reasonable to conclude that they are formed in the lymph-nodes. If they were formed in some organ more deeply situated than the lymph-nodes, there ought to be equal potentiation when the antigens are applied to different sites, but this is not so. J. F. S.

INVENOL IN THE TREATMENT OF PSORIASIS. E. NEUMANN. (1958) *Dermatologica*, 117, 172.

Attempts have been made to treat psoriasis with insulin, because of the reported high glucose content of the affected skin in this disease, but little success has attended these efforts. Neumann, however, thinks that he has had significant results from the oral administration of Invenol (which appears to be identical with Tolbutamide). He reports on 19 patients, aged from 16 to 70, of whom 2 were completely cleared, 14 much improved, 2 moderately improved and only 1 unchanged. J. F. S.